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Solid support mediated chemo and regioselective synthesis of 3*H*-1,5- benzodiazepines from diversely substituted α-oxo ketene dithioacetals†

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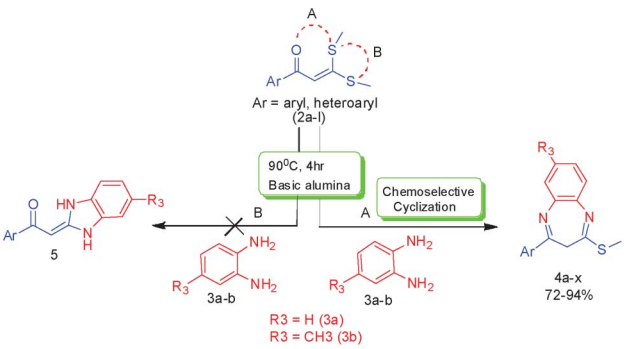
Solvent free, dry media supported synthesis of a series of 4-aryl/heteroaryl-2-methylthio-3*H*-1,5-benzodiazepines by chemo- and regioselective cyclization of substituted α-oxoketene dithioacetals with *o*-phenylenediamines is described. The X-ray crystallographic studies confirmed the formation of the cyclized product.

Benzodiazepines[1–4] have been the target of intense investigation in medicinal chemistry and are now one of the most widely prescribed class of psychotropics[5] due to their remarkable central nervous system (CNS) depressant activity. More recently, the area of biological interest of 1,5-benzodiazepines[6] has been extended to various diseases such as cancer,[7] viral infection (HIV)[8] and cardiovascular disorders.[9] The 1,5-benzodiazepine core is indeed a "privileged scaffold"[10] found in compounds active against a variety of target types including peptide hormones such as cholecystokinin (CCK),[11] interleukin converting enzymes (ICE)[12] and potassium blockers (I_k).[9b] Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be exploited in the synthesis of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[13] Thus, to develop the synthetic strategy of this heterocyclic nucleus is of current importance. In this context, we studied the reaction of α-oxoketene dithioacetals with *o*-phenylenediamines and obtained 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines in high yields.

4-Aryl-2-methylhio-3*H*-1,5-benzodiazepines have been reported to be synthesized by the methylation of 1,5-benzodiazepin-2-thione[14,15] and by using *o*-phenylenediamine as starting materials.[16,17] However, the former afforded the desired products only in the impure state, while the latter required high thermal conditions and a prolonged reaction time (10 h). In view of the reported limitations in the synthesis of 3*H*-1,5-benzodiazepines and necessity for the development of a more efficient, convenient and environmentally friendly methodology, we describe herein a solid state approach for the rapid synthesis of 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines by chemo and regioselective cyclization of α-oxo ketene dithioacetals with *o*-phenylenediamines **3a**/**3b** (Scheme 1). All the α-oxo ketene dithioacetals were synthesized by a reported procedure.[18] Solid phase reactions are of growing interest[19] because of their ease of execution and work-up, mild reaction conditions, rate of reaction, selectivity, high yields, lack of solvents and low cost in comparison to their homogeneous counter parts.

The reaction has been performed under neat conditions by varying different parameters which include solid supports such as (i) acidic, basic or neutral aluminas, (ii) strongly acidic montmorillonite KSF, (iii) silica gel, and solvents such as toluene, ethanol, xylene. From the results obtained it is obvious that basic alumina (Table 1) is the most effective and simplest solid support for the synthesis of **4a**, since a comparatively higher yield is obtained in shorter reaction time by this method. Consequently, we have used same conditions to synthesize a series of aryl **4b–r** (Table 2) and heteroaryl substituted **4s–x** (Table 3) 3*H*-1,5-benzodiazepines.

In order to compare the efficiency of various inorganic supports, a model reaction between 1-(4-fluorophenyl)-3,3-bis (methylthio)prop-2-en-1-one (**2a**) and *o*-phenylene diamine (**3a**)



Scheme 1 Chemoselective cyclization for the synthesis of 3*H*-1,5-benzodiazepines.

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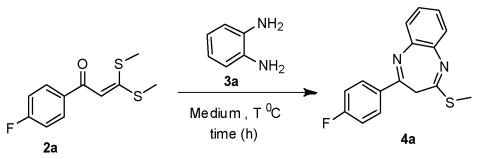
† Electronic supplementary information (ESI) available: Data and spectral copies of ^{1}H, ^{13}C NMR for target compounds. X-ray crystallographic data of compound **4c**. CCDC 920827. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra43347a

Table 1 Optimization of reaction conditions[a]



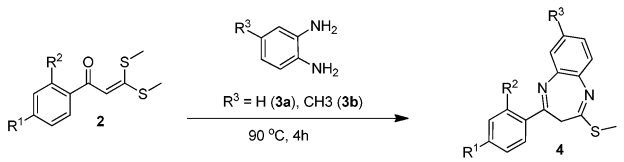
Entry	Medium	T (°C)	Time (h)	Yield[b] (%)
1	Montmorillonite KSF	90	4	5
2	Silica Gel	90	4	42
3	Acidic Alumina	90	4	45
4	Neutral Alumina	90	4	60
5	Basic Alumina	90	4	92
6	Basic Alumina	100	4	90
7	Basic Alumina	90	4	70[c]
8	—	90	4	5
9	Toluene	reflux	8	60
10	Ethanol	reflux	10	62
11	Xylene	reflux	24	58

[a] The reactions were performed using α-oxo ketene dithioacetal **2a** (1 mmol), amine **3a** (1.5 mmol) and inorganic solid support (1 g). [b] Yield of the isolated product after column chromatography. [c] 0.5 g of basic alumina was used.

was performed at 90 °C for 4 h (Table 1). The yield of the product **4a** was lowest when highly acidic montmorillonite KSF was used as a solid support (entry 1) in comparison to silica gel and acidic alumina which gave 42% and 45% yield respectively (entries 2,3). When neutral alumina was used it led to the formation of **4a** in 60% yield (entry 4). It is highly notable that the reaction of **2a** and **3a** gave the highest yield of 92% in basic alumina as an inorganic support (entry 5). To the best of our knowledge this is the first example in which 3*H*-1,5-benzodiazepine has been obtained directly and efficiently from **2a** and **3a** by using basic alumina as the reaction medium in the absence of any solvent. It was noticed that when the temperature of the reaction was increased from 90 °C to 100 °C, it had no significant effect on the yield of the product **4a** and almost comparable yield of 90% was obtained (entry 6). Reducing the amount of solid support from 1 g to 0.5 g adversely decreased the yield of **4a** to 70% which was anticipated due to improper adsorption of the reactants on a solid support (entry 7). However in the absence of a solid support, the reactants remained almost unchanged during the course of reaction with a negligible yield of 5% (entry 8).

We also carried out the cyclization reaction of **2a** and **3a** in toluene, ethanol and xylene (entries 9–11), in order to compare

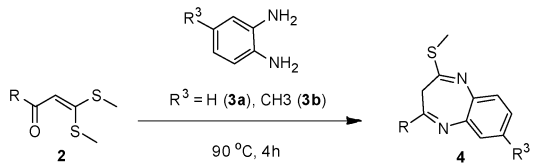
Table 2 Synthesis of various aromatic benzodiazepine derivatives[a]

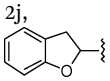
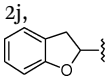
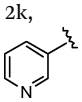
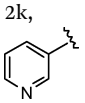


Entry	Substrate (2a–i)	Diamine	Product (4a–r)	Yield[b](%)
1	2a, R^1 = F, R^2 = H	3a	4a	92
2	2a, R^1 = F, R^2 = H	3b	4b	94
3	2b, R^1 = Cl, R^2 = H	3a	4c	85
4	2b, R^1 = Cl, R^2 = H	3b	4d	87
5	2c, R^1 = Br, R^2 = H	3a	4e	88
6	2c, R^1 = Br, R^2 = H	3b	4f	89
7	2d, R^1 = CF_3, R^2 = H	3a	4g	88
8	2d, R^1 = CF_3, R^2 = H	3b	4h	87
9	2e, R^1 = Cl, R^2 = Cl	3a	4i	80
10	2e, R^1 = Cl, R^2 = Cl	3b	4j	82
11	2f, R^1 = CH_3, R^2 = H	3a	4k	85
12	2f, R^1 = CH_3, R^2 = H	3b	4l	90
13	2g,R^1= OCH_3, R^2 = H	3a	4m	78
14	2g,R^1= OCH_3, R^2 = H	3b	4n	77
15	2h, R^1 = H, R^2 = OCH_3	3a	4o	80
16	2h, R^1 = H, R^2 = OCH_3	3b	4p	82
17	2i, R^1 = F, R^2 = OCH_3	3a	4q	85
18	2i, R^1 = F, R^2 = OCH_3	3b	4r	83

[a] The reactions were performed using α-oxo ketene dithioacetal 2 (1 mmol), amine 3 (1.5 mmol) and basic alumina (1 g). [b] yield of the isolated product after column chromatography.

Table 3 Synthesis of various heterocyclic benzodiazepine derivatives[a]



Entry	Substrate (R)	Diamine	Product (4s–x)	Yield[b](%)
1	2j, 	3a	4s	82
2	2j, 	3b	4t	85
3	2k, 	3a	4u	70
4	2k, 	3b	4v	72
5	2l, 	3a	4w	75
6	2l, 	3b	4x	80

[a] The reactions were performed using α-oxo ketene dithioacetal 2 (1 mmol), amine 3 (1.5 mmol) and basic alumina (1 g). [b] Yield of the isolated product after column chromatography.

with organic solvents. It shows that, reactions performed in these solvents proceeded much more slowly and gave lower yields compared to the reaction using basic alumina as a solid support. These results clearly show the advantage of a solid support such as basic alumina over high boiling and hazardous solvents.

With the established optimal conditions (Table 1, entry 5), we explored the scope of α-oxo ketene dithioacetals **2(a–l)** with *o*-phenylenediamines **3a**/**3b**. As shown in Table 2, the reaction was tolerant towards a variety of α-oxo ketene dithioacetals (**2**) bearing different substituents at $\mathbf{R^1}$ **and** $\mathbf{R^2}$. When an electron-withdrawing group was used as $\mathbf{R^1}$, then reaction was well implemented to form intriguing cyclized products **4a–h** in 87–94% yields (entries 1–8). Whereas placement of electron-withdrawing groups at both $\mathbf{R^1}$ and $\mathbf{R^2}$ resulted in 80–82% yield (entry 9–10). When an electron-donating group was used as $\mathbf{R^1}$ then products **4k–n** were obtained in 77–90% yields (entries 11–14), and a comparable yield of **4o**, **4p** was obtained when $\mathbf{R^2}$ was used as electron-donating group (entries 15–16). Furthermore, When $\mathbf{R^1}$ was used as electron-withdrawing and $\mathbf{R^2}$ was used as electron donating in the same compound then the yield was 85% and 83% respectively (entries 17–18).

We further employed the same protocol to examine its scope for the reaction of *o*-phenylenediamine **3a**/**3b** with α-oxoketene dithioacetals bearing heterocyclic rings as **R** (Table 3). Using benzofuran as **R** afforded the products in 82% and 85% yield (entries 1–2) respectively. However when pyridine, thiophene were used as heteroaryl substituents, the corresponding products **4u–x** were obtained in 70–80% yield. (entries 3–6).

Structural assignments have been made on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectra. IR spectra of the products **4a–x** did not reveal characteristic ketocarbonyl absorption peaks in the range 1675–1670 cm^{-1} and also, absorption of primary amino groups (two bands in the region 3450–3150 cm^1) were absent. On another hand, the copresence of an absorption at around 1585–1600 cm^{-1} υ(C=N), and C–H stretching frequencies in the range 2920–2930 cm^{-1} were observed.

In the ^{1}H NMR spectra, absorptions as singlets at δ 3.30–3.60 (s, 2H) and δ 2.40–2.50 (s, 3H), were characterized for methylene protons between two imine bonds and one methyl proton of SCH_3 in **4a–x**. Formation of the final compound **4a** was further confirmed on the basis of ^{13}C NMR and mass spectra. In the mass spectrum of **4a**, the appearance of molecular ion peaks, *m*/*z*, [M + 1] at 285 corresponds to the molecular mass of the compound. Additionally, the structures of the synthesized novel 3*H*-1,5-benzodiazepine derivatives (4) have been confirmed by the single crystal X-ray diffraction analysis of compound **4c** (Fig. 1).

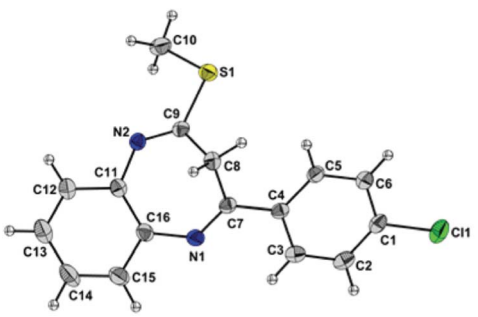
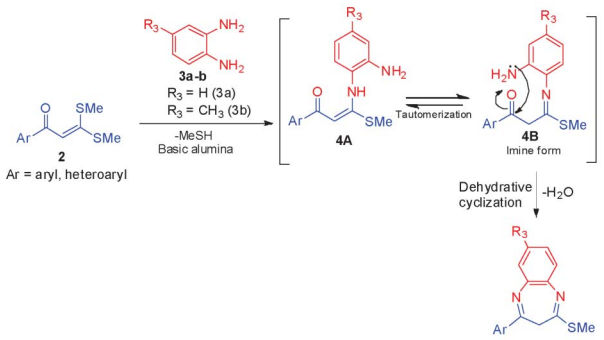


Fig. 1 Ortep diagram of compound **4c**.



Scheme 2 Plausible mechanism for synthesis of 3*H*,1-5 benzodiazepines.

On the basis of above experimental results, a plausible mechanism involving the enamine–imine tautomeric intermediate is depicted as shown in Scheme 2. The mechanism involves substitution of one of the thiomethyl groups of ketene dithioacetal **2** by one of the amino groups of reactant **3a**/**3b** resulting in formation of intermediate **4A** at first. This intermediate can either be converted into ketene aminal **5**[20] (Scheme 1), or tautomerise to the imine form **4B**. **4B** is likely to exist in an *anti*-configuration due to steric stability and undergo cyclocondensation yielding **4**. This mechanism can also best interpret the results reported in the literature;[21] especially the reaction between ketene dithioacetals and 2-aminothiophenol[22] or 2-aminophenol[22] in the presence of sodium, and guanidine[22] or hydrazine.[22]

Conclusions

In conclusion, we have developed an efficient, green methodology for the synthesis of 3*H*,1-5 benzodiazepines. The advantages such as (i) no requirement of additional reagent/catalyst, (ii) non-inflammable and nontoxic reaction medium, (iii) high yields, (iv) excellent chemo and regioselectivity, (v) virtually no waste generation, and (vi) ease of product isolation/purification fulfil the triple bottom line philosophy of green chemistry and make the present methodology environmentally benign. Furthermore, the methylthio group can be explored for the synthesis 2-amino-4-aryl-3*H*-1,5-benzodiazepine analogues of biological importance.

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